

Prevention of Lyme Disease Through Active Immunization:

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Summary

This report provides recommendations for use of a newly developed recombinant outer-surface protein A (Osp A) Lyme disease vaccine (LYMERix™, SmithKline Beecham Pharmaceuticals) in persons 15 years of age and older within the United States. The purpose of these recommendations is to provide healthcare providers, public health authorities, and the public with guidance on the risk of acquiring Lyme disease and on the role of vaccine as an adjunct to preventing Lyme disease. The Committee recommends that decisions regarding vaccine use be based on assessment of individual risk, taking into account both geographical risk and a person's activities and behaviors relating to tick exposure.

INTRODUCTION

Lyme disease is a tick-borne zoonosis caused by infection with the spirochete, *Borrelia burgdorferi*. The number of annually reported cases of Lyme disease in the United States has increased about 25-fold since national surveillance began in 1982, and a mean of approximately 12,500 cases annually was reported by states to the Centers for Disease Control and Prevention (CDC) from 1993 - 1997 (1, 2). In the United States, the disease is mostly localized to states in the northeastern, mid-Atlantic, and upper north-central regions, and to several counties in northwestern California.

Lyme disease is a multi-system, multi-stage, inflammatory illness. In its early stages, the disease is readily cured with oral antibiotics; however, untreated or inadequately treated infection may progress to late-stage rheumatological or neurological complications requiring more intensive therapy. The first line of defense against Lyme disease and other tick-borne illnesses is avoidance of tick infested habitats, use of personal protective measures such as repellents and protective clothing, and checking for and removing attached ticks. Early diagnosis and treatment prevents late-stage complications.

Two Lyme disease vaccines have recently been developed using recombinant *B. Burgdorferi* lipidated outer surface protein A (rOsp A) as immunogen (LYMERix™, SmithKline Beecham Pharmaceuticals; ImuLyme™, Pasteur Mérieux Connaught). At this time, only LYMERix™ has been licensed by the Food and Drug Administration for use in the United States, and these recommendations apply only to the use of this vaccine. Supplemental statements will be provided as additional Lyme disease vaccines are licensed.

results of a large-scale, randomized, controlled (Phase III) trial of safety and efficacy of LYMERix™ in persons residing in endemic areas of the northeastern and north-central United States indicate that the vaccine is safe and efficacious in persons aged 15 to 70 years when given in a 3-dose schedule at 0, 1, and 12 months (3, 4). Information on vaccine safety and efficacy beyond the transmission season immediately following the third dose is not available, thus the duration of protective immunity and need for booster doses beyond dose 3 are not known.

CLINICAL FEATURES OF LYME DISEASE

Clinical Description

Lyme disease most often presents with a characteristic rash, erythema migrans, accompanied by nonspecific symptoms such as fever, malaise, fatigue, headache, myalgia, and arthralgia (5-7). The incubation period from infection to onset of erythema migrans is typically 7 to 14 days but may be as short as 3 days and as long as 30 days. Erythema migrans is observed in 85% or more of patients with early symptomatic infection (6); however, a small proportion of infected individuals have no recognized illness (asymptomatic infection determined by serological testing), or manifest only non-specific symptoms suggesting viral illness, such as fever,

headache, fatigue, and myalgia.

Lyme disease spirochetes disseminate from the site of inoculation by cutaneous, lymphatic and blood-borne routes. The signs of early disseminated infection usually occur days to weeks after the appearance of a solitary erythema migrans lesion. In addition to multiple (secondary) erythema migrans lesions, early disseminated infection may be manifest as disease of the nervous system, the musculoskeletal system, or the heart (5-7). Neurologic manifestations include lymphocytic meningitis, cranial neuropathy (especially facial nerve palsy), and radiculoneuritis. Musculoskeletal manifestations may include migratory joint and muscle pains with or without objective signs of joint swelling. Cardiac manifestations are rare but may include transient atrioventricular blocks of varying degree.

Borrelia burgdorferi infection in the untreated patient may progress to late disseminated disease weeks to months after infection (5-7). The most common manifestation of late disseminated Lyme disease is intermittent arthritis of one or a few joints, usually large, weight-bearing joints such as the knee. Less frequently, patients develop chronic axonal polyneuropathy, or encephalopathy, the latter manifested by subtle cognitive disorders, sleep disturbance, fatigue, and personality changes. Infrequently, Lyme disease morbidity may be severe, chronic and disabling, especially if the disease is treated late (8, 9). An ill-defined post-Lyme disease syndrome occurs in some persons following treatment for Lyme disease (10-12).

Lyme disease is rarely, if ever, fatal.

Diagnosis

Persons with known endemic exposure and physician-diagnosed erythema migrans should be treated for Lyme disease without serologic testing. Erythema migrans should be clinically differentiated from similar rashes that are not caused by *B. burgdorferi* infection. In areas of low or no endemic risk, the likelihood of Lyme disease in a patient with an erythema migrans-like rash is low. Serologic testing may be useful when patients with endemic exposure present with manifestations of disseminated Lyme disease without erythema migrans. Negative test results are useful in ruling out Lyme disease in patients with clinical findings compatible with disseminated or late-stage infection (13). Since the proportion of false positive results increases when the pretest probability of Lyme disease is low, the use of testing to make a diagnosis of Lyme disease in individuals without endemic exposure is not recommended (13).

When serologic testing is indicated, CDC recommends testing initially with a sensitive first test, either an enzyme-linked immunosorbent assay (EIA) or an indirect fluorescent antibody (IFA) test; followed by testing with the more specific Western immunoblot (WB) test to corroborate equivocal or positive results obtained with the first test (14). Although antibiotic treatment in early localized disease may blunt or abrogate the antibody response, patients with early disseminated or late-stage disease almost always have strong serological reactivity and demonstrate expanded WB IgG banding patterns to diagnostic *B. burgdorferi* antigens (15, 16).

Antibodies often persist for months or years following successfully treated or untreated infection. Thus seroreactivity alone cannot be used as a marker of active disease. Neither positive serologic test results nor a history of previous Lyme disease assure that an individual has protective immunity. Repeated infection with *B. burgdorferi* has been documented (17).

Borrelia burgdorferi can be cultured from 80% or more biopsy specimens taken from early erythema migrans lesions (18). However, the diagnostic usefulness of this procedure is limited because of the need for a special bacteriologic medium (modified Barbour-Stoenner-Kelly medium) and protracted observation of cultures. Polymerase chain reaction (PCR) has been used to amplify genomic DNA of *B. burgdorferi* in skin, blood, CSF, and synovial fluid (19, 20), but PCR has not been standardized for routine diagnosis of Lyme disease.

Treatment

Lyme disease can usually be treated successfully with standard antibiotic regimens (5, 6). Early and uncomplicated infection, including infection presenting with isolated cranial nerve palsy, almost always re-

sponds satisfactorily to treatment with orally administered antibiotics. Parenteral antibiotics are generally recommended for treating meningitis, later stage neurologic Lyme disease, and complicated Lyme disease arthritis. Late, complicated Lyme disease may respond slowly or incompletely, and more than one antibiotic treatment course may sometimes be required to eliminate active infection (8, 9). Refractory Lyme disease arthritis is associated with the HLA-DR4 haplotype (21), and may require antiinflammatory agents and surgical synovectomy for relief of symptoms (8). A minority of patients have persistent or recurrent symptoms following appropriate antibiotic therapy (“chronic Lyme disease”, “post-Lyme syndrome”). These symptoms may be due to causes other than persisting infection (21, 22).

EPIDEMIOLOGY OF LYME DISEASE

Antigenic variation of *B. burgdorferi* sensu lato

In the United States, a number of genospecies of *B. burgdorferi* sensu lato have been isolated from animals and ticks, but only OspA expressing *B. burgdorferi* sensu stricto has been isolated from humans (23), and existing evidence suggests that rOspA vaccines will be protective against most if not all human infections in the United States (24). *B. burgdorferi* sensu stricto also occurs in Europe, but the dominant European and Asian genospecies are *B. garinii* and *B. afzelii*, both of which antigenically distinct from *B. burgdorferi* sensu stricto (25), and vary in their expression of OspA. Vaccines using combinations of immunogenic proteins may be necessary to provide protection against multiple genospecies (26).

Routes of Transmission

Borrelia burgdorferi infection is acquired from infected ticks at the time they take a blood meal (27), and not by person-to-person spread or direct contact with infected animals. Transplacental transmission of *B. burgdorferi* has been reported (28, 19), but the effects of such transmission on the fetus remain unclear. The results of several epidemiologic studies suggest that congenital Lyme disease must be extremely rare if it occurs at all (30, 31). Transmission in breast milk has not been described. Although *B. burgdorferi* can be cultured from the blood in some patients with early acute infection, and is able to survive for several weeks in stored blood, the risk of transfusion acquired infection is thought to be minimal (32).

Tick Vectors of Lyme Disease

Borrelia burgdorferi is transmitted to humans by ticks of the *Ixodes ricinus* complex (33). *Ixodes scapularis* (the black-legged, or deer tick) is the vector in the eastern United States; *I. pacificus* (the western black-legged tick) transmits *B. burgdorferi* in the western United States (34, 35). *Ixodes scapularis* is a vector for human granulocytic ehrlichiosis and babesiosis (33, 36). In their nymphal stage, these ticks feed predominantly in the late spring and early summer. The majority of Lyme disease cases result from bites by infected nymphs. In highly enzootic areas of the United States, approximately 15-30% of questing *I. scapularis* and up to 14% of *I. pacificus* nymphs are infected with *B. burgdorferi* (37-40). However, in the southern United States, the prevalence of infection in *I. scapularis* ticks is generally 0-3% (35). The risk of acquiring Lyme disease in the United States varies with the distribution, density and infection prevalence of vector ticks (Figure 1).

Over the past several decades, the distribution of *I. scapularis* has spread slowly in the northeastern and upper north-central regions of the United States (41). Although deer are incompetent reservoirs of *B. burgdorferi*, they are the principal maintenance hosts for adult black-legged ticks, and the presence of deer appears to be a pre-requisite for the establishment of *I. scapularis* in any area (42). The explosive repopulation of the eastern United States by white-tailed deer in recent decades has been linked to the spread of *I. scapularis* ticks and of Lyme disease in this region. The future limits of this spread are not known (41).

Distribution of Human Cases of Lyme Disease

Lyme disease is endemic in several regions in the United States, Canada and temperate Eurasia (1, 43). Lyme disease accounts for more than 95% of all reported cases of vector-borne illness in the United States. Using a national surveillance case definition (44), more than 62,000 cases were reported by states to the CDC from 1993 - 1997, and the national mean annual rate in this 5-year period was 5.5 cases per 100,000 population (CDC, unpublished). Persons of all ages are thought to be equally susceptible to infection, although the highest reported rates of Lyme disease occur in children aged <15 years of age, and in adults aged 30-59 years (1). Both under-reporting and overdiagnosis are common (45-47). Although cases of Lyme disease have been reported by 48 states, only 13 states are considered by CDC to be either highly or moderately endemic, and risk is thought to be low or non-existent in the remaining 37 states and the District of Columbia (Table 1). More than 90% of cases are reported by about 150 countries in these 13 high and moderate risk states, which are located along the northeastern and mid-Atlantic seaboard and in the upper north-central region of the United States (Figure 1).

A rash similar to erythema migrans of Lyme disease, but not caused by *B. burgdorferi* infection, has been described in patients who have been bitten by ticks in the southern United States (48, 49). This rash is suspected to be associated with the bite of *Amblyomma americanum* ticks (50), and there is no evidence that patients with the rash develop disseminated disease.

Populations at Risk of Lyme Disease

Most *B. burgdorferi* infections are thought to result from peri-residential exposure to ticks (37, 51-54) during property maintenance, recreation, and leisure activities. Thus, individuals who live or work in residential areas surrounded by woods or overgrown brush infested by vector ticks are at risk of getting Lyme disease. In addition, persons who participate in recreational activities away from home such as hiking, camping, fishing and hunting in tick habitat, and persons who engage in outdoor occupations, such as landscaping, brush clearing, forestry, and wildlife and parks management in endemic areas may also be at risk of getting Lyme disease (55-57).

PREVENTION AND CONTROL OF LYME DISEASE

Avoidance of Tick Habitat

Whenever possible, persons should avoid entering areas that are likely to be infested with ticks, particularly in spring and summer when nymphal ticks feed. Ticks favor a moist, shaded environment, especially that provided by leaf litter and low-lying vegetation in wooded, brushy or overgrown grassy habitat. Both deer and rodent hosts must be abundant to maintain the enzootic cycle of *B. burgdorferi*. Sources for information on the distribution of ticks in an area include state and local health departments, park personnel, and agricultural extension services.

Personal Protection

Individuals who are exposed to tick infested areas should wear light-colored clothing so that ticks can be spotted more easily and removed before becoming attached. Wearing long sleeved shirts and tucking pants into socks or boot tops may help keep ticks from reaching the skin. Ticks are usually located close to the ground, so wearing high rubber boots may provide additional protection. Application of insect repellents containing DEET (n,n-diethyl-m-tolamide) to clothes and exposed skin, and permethrin (which kills ticks on contact) to clothes, should also help reduce the risk of tick attachment. DEET can be used safely on children and adults but should be applied according to Environmental Protection Agency guidelines to reduce the possibility of toxicity (58).

Tick Check and Removal

Since transmission of *B. burgdorferi* from an infected tick is unlikely to occur before 36 hours of tick attachment (27, 59), daily checks for ticks and their prompt removal will help prevent infection.

Prophylaxis after Tick Bite

The relative cost-effectiveness of post-exposure treatment of tick bites to avoid Lyme disease in endemic areas is dependent on the probability of *B. burgdorferi* infection after a tick bite (60). In most circumstances, treating persons with tick bites alone is not recommended (6, 61). Individuals who are bitten by a deer tick should remove the tick and seek medical attention if any signs or symptoms of early Lyme disease, ehrlichiosis, or babesiosis develop over the ensuing weeks.

Strategies to Reduce Tick Abundance

The number of ticks in endemic residential areas may be reduced by removing leaf litter, brush- and wood-piles around houses and at the edges of yards, and by clearing trees and brush to admit more sunlight and reduce the amount of suitable habitats for deer, rodents, and ticks (62). Tick populations have also been effectively suppressed through the application of pesticides to residential properties (63, 64). Community based interventions to reduce deer populations or to kill ticks on deer and rodents have not been extensively implemented, but may be effective in reducing community wide risk of Lyme disease (65). The effectiveness of deer feeding stations equipped with pesticide applicators to kill ticks on deer, and other baited devices to kill ticks on rodents, is currently under evaluation.

Early Diagnosis and Treatment

Lyme disease in its early stages is a readily treatable disease (5, 6). The early diagnosis and proper antibiotic treatment of Lyme disease is an important strategy to avoid morbidity and costs of complicated and late-stage illness.

LYME DISEASE VACCINE

Description

LYMERix™ is made from lipidated recombinant outer-surface protein A (rOspA) of *B. burgdorferi* sensu stricto. The rOspA protein is expressed in *Escherichia coli* and purified. LYMERix™ contains 30 µg of purified rOspA lipidated protein absorbed onto aluminum hydroxide adjuvant.

Mechanism of Action

Evidence from several studies in animals indicates that *B. burgdorferi* in a vector tick undergoes substantial antigenic change between time of tick attachment on a mammalian host and subsequent transmission of the bacterium to the host. The spirochetes residing in the tick gut at the initiation of tick feeding express primarily OspA. As tick feeding begins, the expression of outer-surface protein C (OspC) is increased and the expression of OspA is decreased, so that spirochetes that reach the mammalian host after passing through the tick salivary glands express primarily OspC (66). The rOspA vaccine appears to exert its principal protective effect by neutralizing or killing Lyme disease spirochetes within the tick gut (67).

Route of Administration, Vaccination Schedule, and Dosage

0.5ml (30 µg) of LYMERix™ is administered by intramuscular injection into the deltoid muscle. Three doses are required for optimal protection, with the initial dose followed by a second dose one month later and a third dose 12 months after the first. Vaccine administration should be timed so that the second dose of the vaccine (year one), and the third dose (year two) are given several weeks before the beginning of the *B. burgdorferi* transmission season, which usually begins in April.

VACCINE PERFORMANCE

Safety

Randomized, Controlled Clinical (Phase III) Trial of LYMERix™ (3). A total of 10,936 subjects aged 15 to 70 years living in Lyme disease endemic areas were recruited at 31 sites and randomized to receive 3 doses of vaccine or placebo. 5469 subjects received at least one 30 µg doses of rOspA vaccine with adjuvant, and 5467 subjects received at least one injection of placebo. The subjects were then followed for a period of 20 months. Information on adverse events that were felt to be related or possibly related to injection were available from 4999 subjects in each group. Soreness at the injection site was the most frequently reported adverse event, reported without solicitation by 24.1% of vaccine recipients and 7.6% of placebo recipients ($p < 0.001$). Redness and swelling at the injection site were reported by less than 2% of either group but were significantly more frequent among vaccine recipients than among those who received placebo. Myalgia, influenza-like illness, fever, and chills were significantly more common among vaccine recipients than placebo recipients, but none of these was reported by more than 3.2% of subjects (3). Reports of arthritis were not significantly different between vaccine and placebo recipients, but vaccine recipients reported significantly more transient arthralgia and myalgia following each dose of vaccine (SKB, LYMERix™ product label.) There were no statistically significant differences between vaccine and placebo groups in the incidence of adverse events more than 30 days after receiving a dose, and there were no episodes of immediate hypersensitivity among vaccine recipients (3).

Safety in Patients with Previously Diagnosed Lyme Disease. The safety of three different dosage strengths of rOspA vaccine with adjuvant in adults with previous Lyme disease was evaluated in an uncontrolled safety and immunogenicity trial (68). Doses were administered at 0,1, and 2 months. Subjects were followed up to one month after the third dose. No serious adverse events were recorded over the study period.

In the randomized controlled Phase III trial of LYMERix™, the vaccine had a similar safety profile in subjects who reported a history of Lyme disease and in those who did not (3).

Risk for Possible Immunopathogenicity of rOspA Vaccine. Following infection with *B. burgdorferi*, persons who express certain HLA-DR4 subtypes are more likely than others to develop chronic, poorly responsive Lyme arthritis associated with high levels of antibody to OspA in serum and synovial fluid (20). It has been proposed that an autoimmune reaction may develop within the joints of some of these individuals as a result of molecular mimicry between the dominant T cell epitope of OspA and human leukocyte function associated antigen (hLFA-11) (69). The Phase III trial did not detect differences in the incidence of neurological or rheumatologic disorders between vaccine recipients and their placebo controls during the 20 months following the initial dose (3). However, because the association between immune reactivity to OspA and treatment resistant Lyme arthritis is poorly understood, the vaccine should not be administered to individuals with a history of treatment resistant Lyme arthritis.

Efficacy

Randomized, Controlled Trial (Phase III) of LYMERix™. Efficacy in preventing “definite” Lyme disease (erythema migrans, or objective neurologic, musculoskeletal or cardiovascular manifestations of Lyme disease, plus laboratory confirmation of infection by cultural isolation, PCR positivity, or WB seroconversion) in the vaccinated cohort after two doses was 49% (95% CI, 15-69%) and after three doses was 76% (95% CI, 58-86%) (3). Efficacy in protecting against asymptomatic infection (no recognized symptoms, but with WB seroconversions recorded in year 1 or year 2) was 83 % (95% CI, 32-97%) in year 1 and 100% (95% CI, 26-100%) in year 2.

Immunogenicity

A subset of adult subjects enrolled in the Phase III clinical trial of LYMERix™ were studied for the development of OspA antibodies at months 2, 12, 13, and 20 (3). At month 2, one month following the second injection, the geometric mean antibody titer (GMT) of Ig(anti-OspA antibodies was 1227 Elisa units per milliliter. Ten months later, the GMT had declined to 116 ELISA units per milliliter. At month 13, one month after the third injection, a marked anamnestic response resulted in a GMT of 6006 ELISA units per milliliter. At month 20, the mean response had fallen to 1991 ELISA units per milliliter (SKB package insert). An analysis of antibody titers and the risk of developing Lyme disease from a subset of subjects enrolled in protection the Phase III clinical trial suggested that a titer above 1200 ELISA Units/ml correlated with protection (SKB poster at IDSA, November 1998).

Effect of Vaccination on the Serologic Diagnosis of Lyme Disease

Care providers and laboratorians should be advised that vaccine induced anti-rOspA antibodies routinely causes falsely positive EIA results for Lyme disease(70). Experienced laboratory workers, through careful interpretation of the results of Western immunoblotting, can usually discriminate between *B. burgdorferi* infection and previous rOspA immunization, since most patients do not develop anti-OspA antibodies following natural infection.

COST EFFECTIVENESS OF LYME DISEASE VACCINATION

Although the cost of Lyme disease to society and third party payers has been evaluated (71), there has been no published evaluation of the cost effectiveness of Lyme disease vaccination. CDC has evaluated the cost-effectiveness of vaccination from a societal perspective (CDC, unpublished). At an assumed cost of vaccination of \$100/individual/year, a vaccine efficacy of 0.85, a probability of 0.85 of correctly identifying and treating early Lyme disease, and an assumed incidence of Lyme disease of 1,000 per 100,000 persons per year, the net cost of vaccination to society was \$5,692 per case averted and \$35,375 per complicated neurologic or arthritic case avoided. Of the variables examined, the incidence of Lyme disease had the greatest impact on cost-effectiveness of vaccination. Under baseline assumptions, the societal cost of vaccination exceeds the cost of not vaccinating unless the incidence of Lyme disease is above 1,000 per 100,000. The impact of varying assumptions on the cost-effectiveness of vaccination is shown Figure 2. The likelihood of early diagnosis and treatment also has a substantial impact on vaccine cost-effectiveness because of the reduced incidence of sequels when patients are diagnosed and treated early in their disease.

Most endemic states and counties report Lyme disease incidence rates that are well below 1,000 per 100,000 persons per year. For example, in 1997, the highest reported state incidence rate was 70 per 100,000 in Connecticut, and the highest reported county incidence rate was 500 per 100,000 population in Nantucket County, Massachusetts. However, some studies suggest that only about 10-15% of physician- diagnosed cases

of Lyme disease are reported to state authorities in highly endemic areas (45,46). Epidemiologic studies of high risk populations in the northeastern United States have estimated annual incidence rates above 1,000 per 100,000 in several communities (72-75).

ASSESSING THE RISK OF LYME DISEASE

The decision to administer Lyme disease vaccine should be based on an assessment of individual risk, which depends on a person's likelihood of being bitten by tick vectors infected with *B. burgdorferi*. This likelihood is primarily determined by the density of vector ticks in the environment (which varies by place and season), the prevalence of *B. burgdorferi* infection in vector ticks, and by the extent of person-tick contact, which is related to the type, frequency, and duration of a person's activities in a tick infested environment.

The assessment of risk should first consider the geographical distribution of Lyme disease. The areas of highest Lyme disease risk in the United States are concentrated within a few northeastern and north-central states. A classification of overall Lyme disease risk by state is shown in Table 1. The risk of Lyme disease differs greatly not only between regions and states and counties within states (as shown in Figure 1), but even within counties and townships. Detailed information on the distribution of Lyme disease risk within specific areas is best obtained from state and local public health authorities.

the second step in determining Lyme disease risk is to assess the individual's activities. High risk activities are those that involve frequent or prolonged exposure to the habitat of infected ticks at times of the year when the nymphal stages of these ticks are actively seeking hosts, which in endemic areas is from April through July. Typical habitats of *Ixode* ticks are wooded, brushy, or overgrown grassy areas that are favorable for deer and the tick's rodent hosts. Various recreational, property maintenance, occupational or leisure pursuits that are carried out in tick habitat may be high-risk activities.

When in highly endemic areas, individuals can reduce their risk of Lyme disease by avoiding tick infested habitat. If exposure to tick infested habitat cannot be avoided, individuals may reduce their risk of infection by applying repellents, wearing protective clothing, and regularly checking for and removing attached ticks.

Individuals who are unlikely to seek medical care for early manifestations of Lyme disease may be at increased risk for Lyme disease complications. Morbidity from Lyme disease can be significantly reduced detecting and treating the infection in its early stages, since early and correct treatment almost always results in a prompt and uncomplicated cure.

RECOMMENDATIONS FOR USE OF LYME DISEASE VACCINE

Note: Lyme disease vaccine does not protect all recipients against infection with *B. burgdorferi* and offers no protection against other tick-borne diseases. Vaccinated individuals should continue to practice personal protective measures against ticks and should seek early diagnosis and treatment of suspected tick-borne infections. Use of the vaccine will not reduce risk among unvaccinated individuals. Decisions regarding the use of vaccine should be based on individual assessment of the risk of exposure to infected ticks, and on careful consideration of the relative risks and benefits of vaccination compared to other protective measures, including early diagnosis and treatment of Lyme disease. The risk of Lyme disease is focally distributed in the United States. A list of the reported Lyme disease risk in states is relative to the national average is given in Table 1. A map of the approximate nationwide distribution of risk is given in Table 1. A map of the approximate nationwide distribution of risk is shown in Figure 1. Detailed information on the distribution of Lyme disease risk within specific areas is best obtained from state and local health authorities.

Persons at High Risk

Persons at high risk for *B. burgdorferi* infection are those who:

- 1) reside, work, or recreate in areas of high or moderate risk during Lyme disease transmission season
- AND**
- 2) engage in activities (e.g., recreational, property maintenance, occupational, leisure) that result in frequent or prolonged exposure to tick infested habitat.

Lyme disease vaccine should be considered for persons aged ≥ 15 years who are at high risk for *B. burgdorferi* infection.

Persons at Moderate Risk

Persons at moderate risk for *B. burgdorferi* infection are those who:

- 1) reside, work, or recreate in areas of high or moderate risk during Lyme disease transmission season
- AND**
- 2) are exposed to tick infested habitat, **but whose exposure is neither frequent nor prolonged.**

For persons at moderate risk for *B. burgdorferi* infection, Lyme disease vaccine **may be considered**, but the benefit of the vaccination beyond that provided by basic personal protection and early diagnosis and treatment of infection is uncertain.

Persons at Low or No Risk

Persons at low or no risk for *B. burgdorferi* are those who:

- 1) do not reside, work, or recreate in areas of high or moderate risk during Lyme disease transmission season.
- as well as those who**
- 2) do reside, work, or recreate in areas of high or moderate risk during Lyme disease transmission season **BUT have minimal or no exposure to tick infected habitat.**

Lyme disease vaccine is not recommended for persons who are at low risk or no risk for *B. burgdorferi* infection.

Travelers to Areas of High or Moderate Risk

The desirability of vaccination for individuals who travel to areas of high or moderate risk during Lyme disease transmission season depends on the anticipated frequency and duration of their exposure to tick infested habitat, as well as their likelihood of seeking prompt medical attention if signs or symptoms of Lyme disease develop. Vaccination should be considered for travelers to high or moderate risk areas if frequent or prolonged exposure to tick habitat is anticipated, or if the likelihood of obtaining prompt medical attention for Lyme disease is low. All travelers to high or moderate risk areas should practice personal protection measures as described earlier, and seek prompt diagnosis and treatment if signs or symptoms of Lyme disease develop.

Vaccination Use in Children <15 Years

LYMERix™ is licensed for use in individuals 15 to 70 years of age. Until the safety and immunogenicity of rOspA vaccines in children has been established, this vaccine should not be administered to children <15 years of age.

Vaccination Use in Individuals over 70 Years of Age

Safety and efficacy of LYMERix™ has not been established in individuals over 70 years of age, and LYMERix™ is licensed for individuals 15 to 70 years only. The vaccine is not recommended for individuals over 70 years of age.

Vaccine Use in Pregnancy

There is no evidence that pregnancy increases the risk of Lyme disease or its severity. Acute Lyme disease in pregnancy responds well to antibiotic therapy, and adverse fetal outcomes have not been reported in pregnant women receiving standard courses of treatment. Since safety of rOspA vaccines administered during pregnancy has not been established, vaccination of women who are known to be pregnant is not recommended.

Vaccine Schedule, including Spacing and Timing of Administration

Three doses of the vaccine should be administered by intramuscular injection. The initial dose should be followed by a second dose 1 month later and a third dose 12 months after the first. Vaccine administration should be timed so that the second dose of the vaccine (year one), and the third dose (year two) are given several weeks before the beginning of the *B. burgdorferi* transmission season, which usually begins in April.

Boosters

Whether protective immunity will last longer than one year beyond the month 12 dose is unknown. Data on antibody levels during a 20-month period after the first injection of LYMERix™ suggest that boosters beyond the month 12 booster may be necessary (see “**Immunogenicity**”. p. 11). Further data are needed to make recommendations on vaccination with more than 3 doses of rOspA vaccine.

Simultaneous Administration with other Vaccines

Safety and efficacy of the simultaneous administration of rOspA vaccine with other vaccines has not been established. If LYMERix™ must be given concurrently with other vaccines, each vaccine should be administered in a separate syringe at a separate injection site.

Persons with Immunodeficiency

Persons with immunodeficiency were excluded from the Phase III safety and efficacy trial, and there are no data on Lyme disease vaccine use in this group.

Persons with previous history of Lyme disease

Vaccination should be considered for persons with a history of previous uncomplicated Lyme arthritis who are at continued high risk. Individuals who have treatment resistant Lyme disease should not be vaccinated because of the association between this condition and immune reactivity to OspA.

FUTURE CONSIDERATIONS

Recommendations for surveillance, Research, Education, and Program Evaluation Activities

- Determination of safety, immunogenicity, and efficacy in children.
- Research to determine optimal dosage schedules and timing of administration.
- Research to determine the need for and spacing of booster doses
- Determination of safety and efficacy in persons > 70 years of age.
- Research to develop serodiagnostic tests that discriminate between infection and vaccine-induced antibody production.
- Development of a program of Lyme disease vaccine education for care-providers and prospective vaccine clients.
- Development of an information sheet to be distributed to prospective vaccine recipients or to persons at the time of vaccine administration.
- Surveillance for rare or late-developing adverse effects of vaccination.
- Establishment of post-licensure epidemiologic studies of safety, efficacy, prevention-effectiveness, cost-effectiveness and patterns of use.
- Develop a program to monitor vaccine use at the local and national level and to measure its public health and economic impact.
- Develop population-based studies to assess the impact of vaccine use on incidence of Lyme disease in communities.
- Continue to develop maps of geographical distribution of Lyme disease with improved accuracy and predictive power.

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Table 1. Lyme Disease Risk by State*

High Risk States	Moderate Risk States	Low Risk States	No Risk States
Connecticut	Maine	Alabama	Alaska
Delaware	Massachusetts	Arizona	Colorado
Maryland	Minnesota	Arkansas	Hawaii
New Jersey	New Hampshire	California	Idaho
New York	Vermont	District of Columbia	Montana
Pennsylvania		Florida	Nebraska
Rhode Island		Georgia	New Mexico
Wisconsin		Illinois	North Dakota
		Indiana	Wyoming
		Iowa	
		Kansas	
		Kentucky	
		Louisiana	
		Michigan	
		Mississippi	
		Missouri	
		Nevada	
		North Carolina	
		Ohio	
		Oklahoma	
		Oregon	
		South Carolina	
		South Dakota	
		Tennessee	
		Texas	
		Utah	
		Virginia	
		Washington	
		West Virginia	

*States designated as high risk had, in the period 1993-1997, annual incidences of reported cases of Lyme disease at the level of the national average rate (4.7 per 100,000 population) or greater; those designated as moderate risk had an incidence of reported cases less than the national average rate for the period but greater than half the national rate, and ranged from 2.04-4.61 per 100,000 population; those designated as low risk are states with reported populations of vector ticks (*I. Scapularis* or *I. Pacificus*) but incidence rates of reported cases less than half the national rate; and, states designated as no risk states have no known populations of vector ticks.

Figure 1. National Lyme disease risk map with 4 categories of risk: **Class 1 (high risk)** identifies counties in the to 10 percentile by numbers of cases of Lyme disease reported to CDC form 1994-1995, and where *I. Scapularis* or *I. Pacificus* populations have been established* and have a high prevalence of infection** with *Borrelia burgdorferi*. **Class 2 (medium risk)** identifies all other counties where *I. Scapularis* or *I. Pacificus* populations have been established with a high prevalence of infection. **Class 3 (low risk)** identifies counties where *I. Scapularis* or *I. Pacificus* populations have been established, but infection prevalence is low; or where *I. Scapularis* populations have been reported but not established. **Class 4 (no risk)** identifies counties where neither *I. Scapularis* or *I. Pacificus* have been established or reported. **Note: This map demonstrates an approximate distribution of relative Lyme disease risk in the United States. The true relative risk in any given county compared to other counties may differ from that shown here and may change from year to year. Information on risk distribution within states and counties is best obtained from state and local public health authorities.**

Figure 2. Cost effectiveness of Lyme disease vaccination. This graph shows the effect of variations in cost of vaccination, vaccine effectiveness, and the probability of contracting Lyme disease on cost effectiveness of vaccination. The left hand y-axis measures cost per case of Lyme disease averted. The right hand y-axis measures the cost per long-term sequelae (cardiac, neuralgic, and musculoskeletal) averted. Underlying assumptions are as follows: probability of identifying and treating early Lyme disease, 0.85; cost of treating cardiac sequelae, \$6,845; cost of treating neurological sequelae, \$61,193; cost of arthritis \$34,304; cost of treating early Lyme disease without sequelae \$161).

data derived from *I. scapularis* and *I. Pacificus* distributions in Dennis DT, Nekemoto TS, Victor JC, et al. Reported distribution of *Ixodes scapularis* or *Ixodes pacificus* (Acari: Ixodidae) in the United States. J Med Entomol 1998;35:629-38, and modified by a GIS-based smoothing technique to minimize the effect of missing data.

**Data on infection prevalence in ticks is based upon a combination of published and unpublished reports, and the ratio of competent or non-competent reservoir hosts present in each county as determined from range distribution maps for vector host species.